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Seroepidemiology Of Human Herpesvirus-6 In Different Age Groups In Istanbul

İstanbul'da Human Herpesvirus-6'nın Farklı Yaş Gruplarında Seroepidemiyolojisi

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ABSTRACT

Objective: This research aimed to elucidate the HHV-6 IgM and HHV-6 IgG antibodies in febrile and healthy individuals using ELISA to determine the distribution rates of HHV-6 antibodies in Istanbul.
Method: This research has enrolled 149 individuals *(Group 1)* admitted to the hospital with fever and had at least two symptoms, such as sore throat, swollen lymph nodes, and increased leukocyte count together with fever, with suspicion of herpes infection and 121 healthy individuals *(Group 2)* who had no complaints or findings and were admitted to the hospital for routine check-ups—the presence of HHV-6 Ig M and HHV-6 Ig G antibodies in two different groups.
Results: According to the study, HHV-6 IgG antibody was detected in 86 *(57%)*, and HHV-6 IgM antibody in 28 *(19%)* of 149 febrile individuals. HHV-6 IgM antibody was detected in febrile patients. HHV-6 IgG antibody was found in 48% of healthy individuals, and HHV-6 IgM antibody in 6%. HHV-6 IgM was not detected among healthy individuals in the 0-5 month group. The findings were consistent with the HHV-6 IgM and HHV-6 IgG rates reported in the literature. This study shows that HHV-6 was encountered in 48% of healthy individuals.
Conclusion: This study's results are consistent with the information in the literature. Based on the data, it was thought that organ transplant recipients and donors should be evaluated for HHV-6 infection and that HHV-6 infection should not be ignored in children admitted to the hospital with fever.

Keywords: Human Herpes Viruses (HHV-6), Febrile infectious, Ig M, Ig G, Exanthem subitum.

ÖZET

Amaç: Bu araştırma, İstanbul'da HHV-6 antikorlarının dağılım oranlarını belirlemek için ELISA kullanarak ateşli ve sağlıklı bireylerde HHV-6 IgM ve HHV-6 IgG antikorlarını aydınlatmayı amaçlamıştır.
Yöntem: Bu araştırmaya, ateşle hastaneye yatırılan ve boğaz ağrısı, şişmiş lenf düğümleri ve ateşle birlikte lökosit sayısında artış gibi en az iki semptomu olan, herpes enfeksiyonu şüphesi olan 149 kişi (Grup 1) ve herhangi bir şikayeti veya bulgusu olmayan ve rutin kontroller için hastaneye yatırılan 121 sağlıklı kişi (Grup 2) dahil edilmiştir - iki farklı grupta HHV-6 Ig M ve HHV-6 Ig G antikorlarının varlığı saptanmıştır.
Bulgular: Çalışmaya göre, 149 ateşli bireyin 86'sında (%57) HHV-6 IgG antikoru, 28'inde (%19) HHV-6 IgM antikoru tespit edilmiştir. Ateşli hastalarda HHV-6 IgM antikoru tespit edildi. Sağlıklı bireylerin %48'inde HHV-6 IgG antikoru, %6'sında ise HHV-6 IgM antikoru tespit edildi. 0-5 aylık grupta sağlıklı bireylerde HHV-6 IgM tespit edilmedi. Bulgular literatürde bildirilen HHV-6 IgM ve HHV-6 IgG oranlarıyla tutarlıydı. Bu çalışma HHV-6'nın sağlıklı bireylerin %48'inde görüldüğünü göstermektedir.
Sonuç: Bu çalışmanın sonuçları literatürdeki bilgilerle tutarlıdır. Verilere dayanarak organ nakli alıcıları ve donörlerinin HHV-6 enfeksiyonu açısından değerlendirilmesi gerektiği ve hastaneye ateşle başvuran çocuklarda HHV-6 enfeksiyonunun göz ardı edilmemesi gerektiği düşünülmüştür.

Anahtar Kelimeler: İnsan Herpes Virüsleri (HHV-6), Ateşli Enfeksiyöz, Ig M, Ig G, Exanthem Subitum.

INTRODUCTION

Human Herpes virus 6 (HHV-6) belongs to the family Herpesviridae, and it was first identified in 1986 in people with lymphoproliferative diseases. It has been accepted as a new member of the disease-causing viruses such as Herpes simplex types 1 and 2, Varicella-zoster, cytomegalovirus, and Epstein-Barr viruses [1]. Human Herpesvirus 6 is the cause of roseola infantum (Exanthem subitum, 6th disease). Exanthem subitum is an infectious disease prevalent in children between 6 months and 3 years of age [2]. Studies conducted before the identification of HHV-6 provided essential clues about the role of the marked increase in antibody levels in the course of various diseases and the infection and reactivation in individuals with weak immune systems [3]. Studies conducted in multiple countries have found that

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antibody positivity rates are high in patients with AIDS, sarcoidosis, and B-cell lymphoma. HHV-6 infection has been reported in numerous cases of organ transplantation [4].

Human herpesvirus type 6 (HHV-6) causes exanthema subitum (ES), a benign, febrile disease seen in children, especially in the first two years of life. ES is a disease characterized by sudden onset of high fever and the appearance of a rash after the fever subsides. The most common complications in ES patients are central nervous system (CNS) complications such as febrile seizures and encephalitis. After primary infection, HHV-6 can establish a lifelong latency in peripheral blood mononuclear cells, salivary glands, and CNS [5]. Exanthema subitum is also known as roseola infantum, exanthema criticum, sixth disease, pseudorubella, and three-day fever. The disease is a clinical syndrome characterized by a high fever lasting 3-5 days and the appearance of rashes after the fever subsides. The pathogenesis of the disease is not fully known. ES is a disease of the young age group most commonly seen in children between 7-13 months of age. 90% of cases are children under two years of age [6]. Classical ES begins with a fever exceeding 40ºC and lasts 3-5 days (average 3.8 days). It is often accompanied by irritability. Despite this, most children appear active and alert [7]. The differential diagnosis of a child with fever and rash is one of pediatrics's most common and important issues. Viral rash diseases in children often consist of acute infectious diseases that are self-limiting and can resolve without treatment. The two main findings are fever and rash, as in the title. In most cases, the cause is viruses.

HHV-6, in the beta herpesvirus group of human herpes viruses (HHV), is an acute, febrile infectious disease specific to childhood. It is probably transmitted to children through the secretions of adults. Cases are sporadic. It does not cause outbreaks. It is frequently observed in the community. The incubation period is 10-15 days. Antibodies transmitted from the mother are protective. After infection, it infects CD4, CD46 T lymphocytes. The most common finding in primary HHV-6 infections is fever. A rising fever (40°C) and irritability occur following a short prodromal period. Secondary roseola infection can rarely be seen, and this is due to HHV-7 [8]. Laboratory findings may include decreased mean leukocyte, lymphocyte, and neutrophil count, thrombocytopenia, increased liver enzymes, and atypical lymphocytes in the peripheral smear [7, 8].

Within the scope of this research, we aimed to elucidate the HHV-6 IgM and HHV-6 IgG antibodies in febrile and healthy individuals using ELISA to determine the distribution rates of HHV-6 antibodies in Istanbul.

METHOD

This research has enrolled 149 individuals (Group 1) admitted to the hospital with fever and had at least two symptoms, such as sore throat, swollen lymph nodes, and increased leukocyte count together with fever, with suspicion of herpes infection, and 121 healthy individuals (Group 2) who had no complaints or findings and were admitted to the hospital for routine check-ups—the presence of HHV-6 Ig M and HHV-6 Ig G antibodies in two different groups. A total of 270 serum samples were obtained from individuals who applied to the pediatrics and diseases clinic, infectious diseases and clinical microbiology department, skin diseases, and internal medicine department of SSK Göztepe Education Hospital (Table 1). These 270 venous blood samples were centrifuged, and the sera obtained were stored at -20°C.

Cases whose Salmonella slide agglutination test, Brucella (Rose-Bengal) slide agglutination test and Mononucleosis test were negative from the serum samples sent to the laboratory for fever testing were included in the study.

HHV-6 Ig G and Ig M antibodies were investigated using the ELISA method using Milenia HHV-6 Ig M and Milenia HHV-6 Ig G kits available in Bad Nauheim, Germany. These kits were developed to diagnose HHV-6 infection by qualitatively determining Ig M and Ig G antibodies in serum. The microplates used in the test interact with HHV-6A and HHV-6B antigens in the solid phase. Disposable plastic tubes, absorption tubes, and pipette tips were preferred for the study. To prevent false positives

specific to specific Ig G and rheumatoid factors in determining HHV-6 Ig M, sera were examined by diluting them in absorption tubes. An increase in HHV-6 antibodies was observed in primary infections of CMV. Therefore, CMV Ig M was also discussed in the obtained HHV-6 Ig M-positive samples. Serum samples and kit solutions used for the study were brought to room temperature (15-28°C) before use. Sera were diluted 1/101 using a sample dilution solution. Antigen-coated microspheres were added to the microplates, reacted with the sera, and kept for 60 minutes. Then, the washing process was performed four times. Then, the second antibody solution containing the peroxidase enzyme was added, kept for 60 minutes, and rewashed. TMB/substrate solution was added and incubated in the dark for 10 minutes. 100 µl of stop solution was added to each well, and the results were read with a spectrophotometer at 450 nm wavelength within 10 minutes after the stop procedure. The results obtained were compared with positive and negative control sera. Optical density (OD) values were evaluated qualitatively by determining the cut-off point (OD cut-off). Positive results were accepted as 10% above the cut-off point, and negative results as 10% below the cut-off point.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval with the protocol number, and informed consent has been obtained from all participants.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data and mean and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the “Independent Sample T-test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Table 1. Sources of Serum Collection

Clinics	N	0-5 months		6-11 months		12-23 months		2-14 years,		Adult		Total	
		F	H	F	H	F	H	F	H	F	H	F	H
Pediatric Clinic	133	11	3	19	6	8	13	39	34			77	56
Infectious Diseases Clinic	63	2		1		1	1	9	14	13	22	26	37
Surgery Clinic	13							4		6	3	10	3
Internal Medicine Clinic	61	3	1	1		1		17	17	15	6	36	25
Total	270	16	4	20	7	10	14	69	65	34	31	149	121

F: fever H: healthy.

Using ELISA, the data obtained investigated the presence of HHV-6 Ig M and Ig G antibodies in 270 serum samples. These samples were taken from 0-5 months, 6-11 months, 12-23 months, 2-14 years, and adult groups. In total, 149 of the 270 serum samples were obtained from febrile patients and 121 from healthy individuals. In HHV-6 Ig M positivity, CMV Ig M was negative in febrile patients, while positivity was observed (Table 2). HHV-6-specific Ig G was detected in 57% of febrile patients and Ig M in 19%. The disease incidence rate was determined as 19% and was found to be statistically significant ($p<0.01$). HHV-6 Ig G was found in 48% of healthy individuals, and Ig M was found in only 6% (Table 3). When age groups were examined: 0-5 months, HHV-6 Ig M was not detected in the healthy group. In the febrile group, 6% Ig M + 56% Ig G positivity was observed. Between 6-11 months: Both groups had no HHV-6 Ig M positivity. Ig G positivity differed in the febrile (60%) and healthy (43%) groups. In addition, Ig M+Ig G positivity was detected in 10%. 12-23 months: HHV-6 IgG positivity was found in 60% of the febrile group and 50% in the healthy group. Between 2-14 years:

HHV-6 IgM was limited in the febrile (6%) and healthy (1.5%) groups. IgG positivity was similar in the febrile (36%) and healthy (35%) groups. Ig M + Ig G positivity was observed in the febrile (16%) and healthy (1.5%) groups.

Table 2. Antibody distribution in febrile individuals according to age groups

Age groups	N	Ig G+ lg M+ N	%	IgG+ N	%	lgM+ N	%	IgG (-) lgM (-) N	%	Total lgG+ N	%	Total lgM+ N	%
0-5 months	16	1	6%	9	56%			6	38%	10	62%	1	6%
6-11 months	20	2	10%	12	60%			6	30%	14	70%	2	10%
12-23 months	10			6	60%			4	40%	6	60%		
2-14 years	69	11	16%	25	36%	4	6%	29	42%	36	52%	15	22%
Adult	34	6	18%	14	41%	4	12%	10	29%	20	59%	10	30%
Total	**149**	20	13%	66	44%	8	6%	55	37%	86	57%	28	19%

Adults: Only HHV-6 IgM was found positive in 12% of the febrile group and 3% of the healthy group. IgG positivity was observed in the febrile (41%) and healthy (52%) groups. IgM+IgG positivity was found in the febrile (18%) and healthy (13%) groups.

Table 3. Antibody distribution in healthy individuals according to age groups

Age groups	N	IgG+ lgM+ N	%	IgG+ N	%	lgM+ N %	lgG (-) ve lgM(-) N	%	Total IgG+ N	%	Total lgM+ N	%
0-5 months	4			4	100%				4	100%		
6-11 months	7			3	43%		4	57%	3	43%		
12-23 months	14			7	50%		7	50%	7	50%		
2-14 years	65	1	1,50%	23	35%	1 1,50%	40	62%	24	36,50%	2	3%
Adult	31	4	13%	16	52%	1 3%	10	32%	20	65%	5	16%
Total	**121**	5	4%	53	44%	2 2%	51	50%	58	48 %	7	6%

DISCUSSION

Human herpesvirus 6 has all the characteristic features of the Herpesviridae family. Initially, it was suggested that it be placed in the gammaherpesvirinae subfamily due to its affinity for lymphocytes. Still, it was classified in the beta herpesvirinae subfamily considering its genetic similarity to cytomegalovirus (CMV) and its ability to form inclusions. The differences between the A and B variants of human herpesvirus six have been determined in detail. There are 4% to 25% differences between the genome sequences. These similarities cause intense cross-reactivity between the types [9].

Observations by electron microscopy show that the HHV-6 virus has an icosahedral capsid, envelope, and 162 capsomeres, 160-200 nm in diameter [10]. The approximate diameter of the nucleocapsids is 90 to 110 nanometers [9]. Since HHV-6 is an enveloped virus, it can be quickly inactivated by ether and other lipid solvents. However, it is not resistant to freezing and thawing [1, 2]. It is stable below 37°C but not above 42°C and below pH 6.5 [11]. HHV-6 antigens have been detected in the epithelium of

bronchial glands and saliva. Since infectious HHV-6 has been reported in the saliva of adults, transmission is assumed to occur through oral secretions. [12].

The first infection with HHV-6 usually occurs in children approximately 3-6 months after birth, after maternal antibodies have waned. Most children become seropositive, that is, develop antibodies to the virus, by age 2. It is still unknown how contagious HHV-6 is [13]. The most common childhood disease associated with HHV-6 is exanthema subitum (Roseola infantum, 6th disease). In North America and Europe, perhaps 60-70% of primary infections may be asymptomatic, usually resulting in a mild febrile illness. In Japan, exanthema subitum is diagnosed in approximately 60% of children [14]. Exanthema subitum caused by HHV-6 is characterized by high fever (>39°C) for 3-5 days. This is followed by 1-3 days of rash, blistering, and swollen lymph nodes. In the exanthematous phase of primary infection, lymphocyte increase and neutropenia are frequently observed. The disease is usually overcome without complications. Approximately half of the first febrile illnesses after birth are due to primary infection with HHV-6 [15]. The incubation period is between 5-15 days. The disease usually lasts 2-7 days. HHV-6 virus is sensitive to ganciclovir and foscarnet. Ganciclovir is an antiviral drug that inhibits DNA polymerase, while foscarnet is an antiviral drug that inhibits DNA polymerase and reverse transcriptase [16]. No specific treatment is required for roseola infantum. Antipyretics can be used in cases of high fever, and antiseizure drugs can be used in seizures [17].

Huang et al. used polymerase chain reaction (PCR) to detect HHV-6 DNA in serum and plasma. Their research showed that the PCR test gave positive results with the appearance of HHV-6 Ig G antibodies. This emphasized that detecting HHV-6 DNA in serum by PCR is essential in diagnosing acute or active viral infections [18]. Eizuru et al. investigated the presence of HHV-6 using biopsy samples taken from cervical lymph nodes. Their study detected and demonstrated HHV-6 antigen with the Anticomplement Immunofluorescence (ACIF) method [19]. Another study examined HHV-6 antibody levels using immunofluorescence assay (IFA) and anticomplement immunofluorescence (ACIF) methods by taking smears from the sera of 10 patients. In their study, they found that IFA titers were higher than ACIF. They also reported that the method that can best show the presence of antibodies 5-8 days after infection and is easily understood is IFA for staining [20].

Fox et al. [21] examined the sera of 96 individuals in the past to investigate the presence of HHV-6 and CMV, VZV, EBV, and HSV-IgG antibodies. Their study found no antagonism or cross-reaction between HHV-6 and other herpes viruses. They showed that the indirect immunofluorescence method used to detect HHV-6 IgM and IgG antibodies is specific and that HHV-6 IgM antibodies are found both in the primary infection and reactivation periods [21].

In their previous study, ELISA examined the presence of HHV-6 IgG. In the ELISA test, the lysate of cord blood mononuclear cells infected with HHV-6 was used as an antigen. Different results were obtained with indirect IFA and neutralization tests. The study showed the presence of HHV-6 IgG in all infants. The lowest HHV-6 IgG level was detected in infants aged 3-6 months and increased between 1-2 years of age, reaching a maximum level. It was observed that the prevalence remained almost constant after the age of three [22].

In another study, the HHV-6 IgG avidity test was used to examine primary and recurrent HHV-6 antibody responses in individuals who received organ transplants. In primary HHV-6 infection, changes in antibody avidity were detected, and avidity increased within 5 months. HHV-6 seropositivity was observed in six patients. This test was reported to be valuable in herpesvirus studies in patients who received organ transplants and can distinguish primary from recurrent infections [19].

CONCLUSION

The results of this study are consistent with the information in the literature. Based on the data, it was thought that organ transplant recipients and donors should be evaluated for HHV-6 infection and that HHV-6 infection should not be ignored in children admitted to the hospital with fever.

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AI Statement

The authors used AI and AI-assisted Technologies (Grammarly and MS Word Editor) in the writing process. These technologies improved the readability and language of the work but did not replace key authoring tasks such as producing scientific or medical insights, drawing scientific conclusions, or providing clinical recommendations. The authors are ultimately responsible and accountable for the contents of the whole work.

Competing interests

The authors declare that they have no competing interests.

Consent for Publication

The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

Data Availability

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical Declaration

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Our institution has granted ethics committee approval and informed consent was obtained from all participants.

REFERENCES

1. Grut V, Biström M, Salzer J, et al. Interactions between High Seroreactivity to Human Herpes Virus 6A and Epstein-Barr Virus in MS Development: A Presymptomatic Case-Control Study. Ann Neurol. 2024;96(2):302-305. doi:10.1002/ana.27009

2. Leung AK, Lam JM, Barankin B, Leong KF, Hon KL. Roseola Infantum: An Updated Review. Curr Pediatr Rev. 2024;20(2):119-128. doi:10.2174/1573396319666221118123844

3. Mullins TB, Krishnamurthy K. Roseola Infantum. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 4, 2023.

4. Agut H, Bonnafous P, Gautheret-Dejean A. Human Herpesviruses 6A, 6B, and 7. Microbiol Spectr. 2016;4(3):10.1128/microbiolspec.DMIH2-0007-2015. doi:10.1128/microbiolspec.DMIH2-0007-2015

5. King O, Al Khalili Y. Herpes Virus Type 6. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2023.

6. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev. 2015;28(2):313-335. doi:10.1128/CMR.00122-14

7. Kasai A, Shimizu J, Sato M, Kitamura M, Inaba Y, Motobayashi M. Reduced impact of viral load of HHV-6 in liquor on severity of AESD due to exanthema subitum: A case report and literature review. Brain Dev. 2021;43(8):879-883. doi:10.1016/j.braindev.2021.04.008

8. Agut H, Bonnafous P, Gautheret-Dejean A. Update on infections with human herpesviruses 6A, 6B, and 7. Med Mal Infect. 2017;47(2):83-91. doi:10.1016/j.medmal.2016.09.004

9. Poetranto AL, Wakata A, Tjan LH, Nishimura M, Arii J, Mori Y. Human herpesvirus 6A U27 plays an essential role for the virus propagation. Microbiol Immunol. 2020;64(10):703-711. doi:10.1111/1348-0421.12840

10. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-Shelf Virus-Specific T Cells to Treat BK Virus, Human Herpesvirus 6, Cytomegalovirus, Epstein-Barr Virus, and Adenovirus Infections After Allogeneic Hematopoietic Stem-Cell Transplantation. J Clin Oncol. 2017;35(31):3547-3557. doi:10.1200/JCO.2017.73.0655

11. Lareau CA, Yin Y, Maurer K, et al. Latent human herpesvirus 6 is reactivated in CAR T cells. Nature. 2023;623(7987):608-615. doi:10.1038/s41586-023-06704-2

12. Clark DA. Clinical and laboratory features of human herpesvirus 6 chromosomal integration. Clin Microbiol Infect. 2016;22(4):333-339. doi:10.1016/j.cmi.2015.12.022

13. Munawwar A, Singh S. Human Herpesviruses as Copathogens of HIV Infection, Their Role in HIV Transmission, and Disease Progression. J Lab Physicians. 2016;8(1):5-18. doi:10.4103/0974-2727.176228

14. Arnež M, Avšič-Županc T, Uršič T, Petrovec M. Human Herpesvirus 6 Infection Presenting as an Acute Febrile Illness Associated with Thrombocytopenia and Leukopenia. Case Rep Pediatr. 2016;2016:2483183. doi:10.1155/2016/2483183

15. Yoshizato R, Koga H. Comparison of initial and final diagnoses in children with acute febrile illness: A retrospective, descriptive study: Initial and final diagnoses in children with acute fever. J Infect Chemother. 2020;26(3):251-256. doi:10.1016/j.jiac.2019.09.015

16. Corona-Rodarte E, Torres-Guillen VM, Teran-De-la-Sancha K, Barrera-Godínez A, Gatica-Torres M. Successful management with ganciclovir of drug reaction with eosinophilia and systemic symptoms secondary to antituberculous drugs associated to human herpesvirus-6 reactivation. JAAD Case Rep. 2023;34:90-93. Published 2023 Jan 26. doi:10.1016/j.jdcr.2022.12.021

17. Leung AK, Lam JM, Barankin B, Leong KF, Hon KL. Roseola Infantum: An Updated Review. Curr Pediatr Rev. 2024;20(2):119-128. doi:10.2174/1573396319666221118123844

18. Huang LM, Kuo PF, Lee CY, Chen JY, Liu MY, Yang CS. Detection of human herpesvirus-6 DNA by polymerase chain reaction in serum or plasma. J Med Virol. 1992;38(1):7-10. doi:10.1002/jmv.1890380103

19. Eizuru Y, Minematsu T, Minamishlma Y, Kikuchi M, Yamanishi K, Takahashi M, Kurata T. Human herpesvirus 6 in lymph nodes. Lancet. 1989;1(8628):40-41.

20. Couillard M, Joly JR, Deschênes L, Richer G. Evaluation of variables in immunofluorescence procedures for the detection of antibodies against human herpesvirus 6 (HHV-6). Diagn Microbiol Infect Dis. 1992;15(4):313-320. doi:10.1016/0732-8893(92)90017-n

21. Fox JD, Tedder RS, Birggs EM: Human herpesviruses 6 and 7. " Zuckerman AJ, Banatvala JE,. Pattison JR (eds)" Principles and Practice Clinical Virology 3. press: 135 John Wiley and Sons Ltd, Chichester, New York, Brisbane, Toronto, Singapore

22. Asano Y, Yoshikawa T, Suga S, et al. Enzyme-linked immunosorbent assay for detection of IgG antibody to human herpesvirus 6. J Med Virol. 1990;32(2):119-123. doi:10.1002/jmv.1890320209